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REVIEW

Factors that prognosticate mortality in idiopathic pulmonary arterial hypertension: A systematic review of the literature☆

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Summary
Rationale: There is a lack of consensus on factors that predict mortality in idiopathic pulmonary arterial hypertension (IPAH). Tests that can accurately predict prognosis are needed to guide treatment and counsel patients.
Methods: We conducted a systematic review to identify factors that prognosticate mortality in IPAH. Study design, cohort size, comparison method, measured value, and statistical significance was extracted for eight pre-selected parameters [pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (mPAP), mean right atrial pressure (mRAP), cardiac output, right ventricular end diastolic pressure, functional class, 6 min walk distance (6MWD), and diffusing capacity of carbon monoxide].
Results: 107 factors have been associated with mortality in IPAH. A reproducible predictive association with mortality was demonstrated for only 10 factors: functional class (14 studies), heart rate (10 studies), 6MWD (8 studies), pericardial effusion (5 studies), mPAP (10 studies), mRAP (17 studies), cardiac index (13 studies), stroke volume index (4 studies), PVR (10 studies), mixed venous PaO_2 or saturations (4 studies). Of the 8 factors chosen for detailed

Abbreviations: 6MWD, 6 min walk distance; CO, cardiac output; CI, cardiac index; CPET, cardiopulmonary exercise; DLCO, diffusing capacity of carbon monoxide; IPAH, idiopathic pulmonary arterial hypertension; JTG, John T Granton; JRS, John R Swiston; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NIH, National Institutes of Health; NYHA, New York Heart Association; O_2, oxygen; PAH, Pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PO_2, partial pressure of oxygen; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; RVEDP, right ventricular end diastolic pressure; SRJ, Sindhu R Johnson; WHO, World Health Organization.

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evaluation, there were at least half as many studies that evaluated the variable and did not find an association with mortality compared to those that did.
Conclusions: There is a large body of literature describing numerous factors that predict mortality in IPAH. Most factors have been assessed in very few studies. There are conflicting reports on the prognostic value of many factors. These discrepancies highlight the need to evaluate the literature in total when considering the utility of variables as prognostic factors in IPAH.

Contents

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a disease of unknown etiology characterized by pathological changes in the pulmonary vasculature that lead to increased pulmonary vascular resistance, elevated pulmonary arterial pressures, right ventricular dysfunction, and early death.[1] By consensus IPAH is defined by a mean pulmonary arterial pressures (mPAP) $>$ 25 mmHg at rest, a pulmonary capillary wedge pressure (PCWP) less than 15 mmHg, and an elevated pulmonary vascular resistance (PVR), with no identifiable underlying cause.[2,3]

IPAH is a devastating and progressive condition with a poor long term prognosis.[4] Given the life limiting nature of IPAH, the ability to predict disease progression and death is necessary for optimal care of these patients and timely intervention. This is particularly true given that the treatment of last resort for many patients with IPAH is lung transplantation.[5] This intervention is exquisitely sensitive to timing.[6,7] Lung transplant recipients are also subjected to increase morbidity and mortality and thus transplanting IPAH patients too early may not increase life expectancy.[8] On the other hand, referral for this procedure too late can result in death while awaiting a suitable donor thus deny patients an opportunity for an extended lifespan. Short of transplantation, the most effective intervention for IPAH remains prostacyclin.[5,9] This intervention also require careful consideration of prognosis and timing as it is administered as a continuous parenteral infusion and thus carriers a risk of life threatening complications such as sepsis and hemodynamic collapse if interrupted.[10] Furthermore, many patients are reluctant to initiate this therapy until absolutely necessary as it is cumbersome, labor intensive, and intrusive. With the recent development of oral therapies[5] (such as endothelin receptor antagonists and phosphodiesterase inhibitors) for less severe disease, prognostication has become no less important as timely initiation, escalation, combination, and abandonment of these therapies requires an ability to predict outcome.[11]

There have been significant advances in our pathophysiologic understanding of pulmonary hypertension and the diagnostic classification of this disease has been revised a number of times.[3] These advances, along with the development of new therapeutic and pharmacologic interventions have collectively changed our perspective of IPAH and the evaluation of these patients. During this time a number of new investigative techniques and markers of disease have been developed while older ones have been advanced, refined, and reevaluated.

Despite the growing number of studies evaluating prognosis and prognostic factors for mortality in IPAH, consensus on factors that portend a worse outcome, and the best method or combination of methods of evaluation, remain lacking. In part this is due to the fact that IPAH is a rare and fatal disease. As a result the literature is dominated by small, often retrospective, studies with limited power to properly assess effects or compare multiple outcomes and draw meaningful conclusions. Thus conclusions from individual studies are difficult to draw and extrapolate to larger populations without a comprehensive view of the literature. Consensus statements have provided valuable guidance in the evaluation and management of IPAH patients but have not systematically reviewed the literature to provide a balanced overview of the evidence.[12,13] The purpose of this study is to systematically review the current medical literature to identify factors that prognosticate mortality in IPAH in an attempt to aid clinicians and health care professional in the appropriate evaluation and care of IPAH patients as well as identifying areas in need of further study. Furthermore, a comprehensive review of the literature will facilitate the development of clinically useful composite endpoints for clinical trials and therefore identification of these markers is important not only for patient care and epidemiologic research but also therapeutic clinical trials.

Methods and materials

We performed a literature search using MEDLINE and EMBASE databases (inception to August 2009) to identify original publications describing factors that prognosticate mortality in idiopathic pulmonary arterial hypertension (IPAH). We used the following key terms: "pulmonary hypertension" or "pulmonary arterial hypertension" or "idiopathic pulmonary arterial hypertension" and "mortality" or "survival" or "death", or "prognosis". The search was limited to the English language and human studies. Citations (titles and abstracts) identified from the literature search were reviewed to identify publications relevant to the research question. Complete manuscripts of relevant citations were obtained for full review. References from extracted manuscripts were also reviewed for relevant publications.

Publications were included in the final synthesis if they described baseline factors that were associated with mortality in patients with IPAH. IPAH was defined according to the Venice clinical classification of pulmonary hypertension[13] and was consistent with the Dana Point revised classification.[3] Patient populations defined as primary pulmonary hypertension based on the Evian classification[13] were considered to be synonymous with IPAH and included in the synthesis. Publications were excluded if they did not describe mortality or survival as an outcome, reported a composite endpoint only, did not describe outcomes specifically for IPAH patients (mixed cohorts), or the variables were described in the context of a change over time (with or without treatment) rather than a baseline point evaluation. Case series, interventional studies, observational studies, and population based analyses were all included. Abstracts and case reports were excluded.

Factors associated with mortality in IPAH were collated into 6 domains: history and clinical exam features, exercise parameters, electrocardiographic parameters, clinical investigations [excluding echocardiography (echo) and magnetic resonance imaging (MRI)], non-invasive cardiac parameter (echo and MRI), and invasive hemodymanic parameters. In addition, 8 parameters were selected *a priori* for a more detailed evaluation [PVR, mPAP, mean right atrial pressure (mRAP), cardiac output (CO), right ventricular end diastolic pressure (RVEDP), World Health Organization (WHO) or new York Heart Association (NYHA) functional class, 6 min walk distance (6MWD), and diffusing capacity of carbon monoxide (DLCO)]. These factors were selected by the three authors by consensus. For these parameters, additional information was extracted including the study design, cohort size, comparison method, measured value, and statistical significance. Furthermore, for these 8 parameters all evaluations were extracted regardless of whether a positive association with mortality was identified.

All steps in the literature search were carried out independently by two reviews (JRS and SRJ). Disagreement between the two extracting authors was resolved by consensus. If consensus could not be reached, a third author (JTG) reviewed the study and a decision to include the publication was reach by consensus.

Results

The database search identified 6830 citations (Fig. 1). Review of the titles and abstracts of these citations resulted in 137 publications that were obtained for full review. Six additional studies were identified from the reference

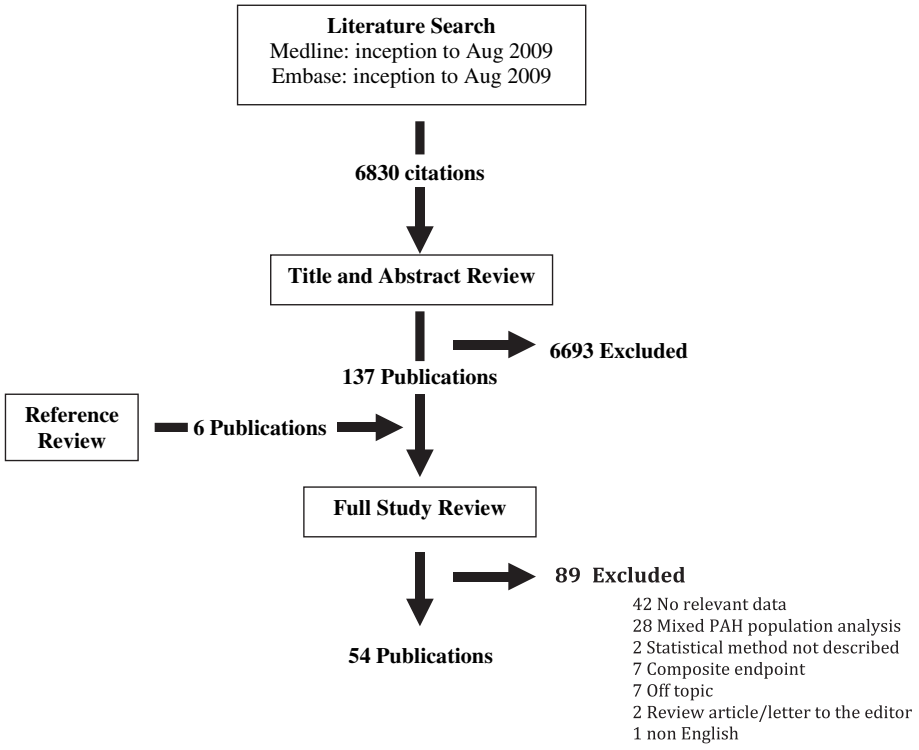

Figure 1 Summary of literature search and identification of publications.

Table 1 Patient factors and findings reported to prognosticate mortality in IPAH.

Parameter	Number of supporting studies	Citation
History and clinical exam		
Sex	1	29
Age at diagnosis	1	39
Age at onset of symptoms	1	39
African—American ethnicity (compared to Caucasian)	1	40
Duration of symptoms at presentation	1	41
Time from onset of symptoms to diagnosis	1	29
Peri-pregnancy presentation	1	20
Initial functional class (WHO or NYHA)	14	4, 14, 15, 18, 19, 21, 22, 25, 29, 33, 39, 42-44
Right heart failure at some stage	2	15, 20
Raynauds phenomenon	2	4
Heart rate (sinus tachycardia)	10	14, 18, 21, 30, 36, 45-49
Exercise parameters		
6 min walk test distance	8	15, 18, 19, 25, 32, 33, 35, 49
6MWT trough SaO_2 during exercise	1	23
6MWT ΔSaO_2 (diff btwn rest and trough SaO_2[5]	1	23
Exercise duration	1	21
Peak VO_2 (mL Kg^{-1} min^{-1})	1	21
Peak systolic blood pressure	1	21
Peak heart rate	1	21
$PETCO_2$ at rest	1	21
VE/VCO_2 slope	1	21
ECG Criteria		
Right ventricular hypertrophy (number of Sokolow and Lyon criteria)	2	16, 50
Right ventricular hypertrophy (WHO criteria)	1	24
Right ventricular hypertrophy (criteria not specified)	2	17, 39
Mean frontal electrical axis of the P wave	3	16, 50, 51
Right axis deviation	1	20
Right atrial strain	1	20
P wave terminal force in V1	1	51
P wave amplitude in lead II	1	24
P wave amplitude in lead III	1	24
P wave amplitude in aVF	1	24
P wave $\geq$0.25 mV in II	1	24
R wave amplitude in V5	2	16, 50
R wave amplitude in V6	2	16, 50
R/*S* ratio in V5	2	16, 50
R/*S* ratio in V6	2	16, 50
qR pattern in V1	2	24, 50
S wave amplitude in V6	2	16, 50
Number of chest leads with *T* wave inversion	1	16
Clinical investigation		
Right ventricular enlargement on chest X-ray	1	20
Cardiothoracic ratio on chest X-ray	1	39
Forced vital capacity	1	27
Forced expiratory volume in 1 s	1	29
Diffusing capacity of carbon monoxide	1	4
Hematocrit	1	52
Platelet activity (spontaneous aggregation)	1	53
D-dimer	1	54
Von Willebrand factor level	1	55
Asymmetrical dimethylarginine concentration	1	56
Serum uric acid	3	21, 57, 58
Plasma atrial natriuretic peptide	2	14, 48

(*continued on next page*)

Table 1 (*continued*)

Parameter	Number of supporting studies	Citation
Plasma brain natriuretic peptide	1	14
Plasma norepinephrine	1	14
N-terminal pro-brain natriuretic peptide	1	25
Perfusion lung scintigraphy (mottled appearance)	1	59
Cardiac ^{123}I-MIBG uptake (heart to mediastinum activity ratio)	1	60
C-reactive protein	1	61
Echocardiography and MRI Parameter		
Severity of pericardial effusion	5	14, 18, 25, 47, 62
Presence of a pericardial effusion	2	18, 25
RA area index (5 cm/m^2)	1	18
Tei index	1	63
RV/LV diastolic area	1	25
LV ejection time	1	64
LV diastolic eccentricity index	1	25
LV systolic eccentricity index	1	25
LV deformity index (longest/shortest diameter of the LV cavity at the point of max deformity in early systole)	2	14, 57
IVC inspiratory diameter	1	25
Pulmonic flow acceleration time $<$62 ms	1	47
Tricuspid early flow deceleration ≤ -300 cm^2/s	1	47
Mitral early flow to atrial flow velocity ratio $\leq$1.0	1	47
Stroke volume index (MRI)[a]	1	19
LVEDVI (MRI)[a]	1	19
RVEDVI (MRI)[a]	1	19
Hemodynamic parameters		
Mean PAP (mmHg)	10	4, 14, 15, 17, 25, 29, 30, 39, 47, 65
Diastolic pulmonary arterial pressure (mmHg)	2	39, 47
Mean right atrial pressure (mmHg)	17	14, 15, 17-19, 21, 25-27, 29, 30, 35, 36, 39, 46, 49, 56
PCWP (mmHg)	1	26
PCWP/left ventricular end diastolic pressure	1	20
Systolic blood pressure (mmHg)	1	26
Systolic PAP/systolic blood pressure	1	26
Cardiac index (L/min/m^2)	13	4, 21, 24, 26-29, 36, 39, 42, 46, 47, 52
Cardiac output (L/min)	3	14, 20, 21
Stroke volume (ml)	1	36
Stroke volume index (ml/beat/m^2)	4	19, 27, 30, 46
Right ventricular work index (kg m/min/m^2)	2	39, 52
Right ventricular stroke work (mmHg cc)	1	36
Right ventricular end diastolic pressure (mmHg)	3	20, 26, 39
Stroke volume/pulmonary pulse pressure (ml/mmHg)	1	36
Mean pulmonary artery·stroke volume (per 100)	1	36
Pulmonary artery/Aortic artery systolic pressure	1	39
Pulmonary pulse pressure (mmHg)	1	36
Pulmonary capacitance (ml/mmHg)	1	36
Reduced pulmonary artery pulsatility (by intravascular ultrasound)	1	66
Increased pulmonary/elastic strain index (by intravascular ultrasound) (mmHg)	1	66
Patent foramen ovale	1	20
Pulmonary vascular resistance (dyn s cm^{-5} or wood units)	10	17, 20, 23-25, 30, 36, 42, 46, 49
Pulmonary vascular resistance index (dyn s cm^{-5} m^{-2} or wood units/m^2)	3	4, 19, 27
Total pulmonary vascular resistance (mPAP/CO/60 $\times$ 1332) (dynes s cm^{-5})	2	26, 52

Table 1 (*continued*)

Parameter	Number of supporting studies	Citation
Systemic vascular resistance (Wood units or dyn s cm^{-5})	3	20, 26, 46
Pulmonary vascular/systemic vascular resistance	3	26, 27, 39
Mixed venous PO_2 (mmHg) or O_2 saturation (%)	4	18, 19, 27, 56
Pulmonary arterial PO_2 (mmHg) or O_2 saturation (%)	2	4, 39
Systemic arterial PO_2 (mmHg) or O_2 saturation (%)	3	21, 39, 52
Systemic venous O_2 saturation (%)	2	14, 21
Arterial-venous O_2 content difference (% or ml/100 ml)	2	21
Arterial PCO_2 (mmHg)	2	29, 30
Acute vasodilator response to prostacyclin	1	67
Acute vasodilator response to calcium channels blockers	1	22

WHO = World Health Organization; NYHA = New York Heart Association; 6MWT = 6 min walk test; CO = cardiac output; O_2 = oxygen; PO_2 = partial pressure of oxygen; PCO_2 = partial pressure of carbon dioxide; ΔSaO_2 = SaO_2 at rest − minimal SaO_2 sustained for >10 s during the 6MWT; VO_2 = oxygen uptake during exercise; $PETCO_2$ = end-tidal partial pressure of carbon dioxide; VE/VCO_2 = ventilation to carbon dioxide production during exercise; MIGB = metaiodobenxylguanidine; RA = right atrium; RV = right ventricle; LV = left ventricle; IVC = inferior vena cava; LVEDVI = LV end diastolic volume index; RVEDVI = RV end diastolic volume index; PAP = pulmonary arterial pressure; mPAP = mean pulmonary arterial pressure; PCWP = post-capillary wedge pressure.

[a] Parameters measured by magnetic resonance imaging (MRI) (all other parameters measured by echocardiography).

lists of these publications. Of these 143 studies, 54 publications described parameters that were associated with mortality in IPAH and were included in the final analysis. From the 54 publications, 107 parameters were identified that were reported to be associated with mortality in IPAH.

Of the 107 parameters identified, there were 11 history and clinical exam features, 9 exercise parameters, 18 electrocardiographic parameters, 18 clinical investigations, 16 non-invasive cardiac parameters (echocardiography and magnetic resonance imaging), and 35 invasive hemodynamic parameters (Table 1). The majority of these factors were reported to be associated with mortality in only a few studies. A predictive association with mortality was reproduced in more than 3 studies for only 10 parameters (Table 2). These 10 parameters were functional class (14 studies), heart rate (10 studies), 6 min walk distance (8 studies), pericardial effusion severity (5 studies), mPAP (10 studies), mRAP (17 studies), cardiac index (13 studies), stroke volume index (4 studies), pulmonary vascular resistance (10 studies), mixed venous partial pressure of oxygen (PO_2) or O_2 saturations (4 studies) (Table 2).

The eight pre-defined parameters that were chosen for a more detailed analysis are shown in Table 3. This table also includes the citations for the studies that found an association of the parameter with mortality as well as the studies that did not. Twenty seven publications reported analyses of the prognostic implications of mPAP for mortality in IPAH. Ten studies found an association between this parameter and mortality while 19 studies did not (Table 4). Two of these studies found an association with mortality in the univariable analysis that was lost when other parameters were corrected for in the mulitvariable analysis.[14,15] One study found an inverse correlation between mortality and mPAP wherein a lower value was associated with a higher mortality.[15] There was significant heterogeneity in the methods of analysis. Within the most common method of evaluation, the Cox proportional hazard model, variations were seen in the analysis with some studies correcting for other variables and other not, some studies using cutoff values for mPAP, and some studies using a per unit analysis (mmHg). Many studies did not report the unit of analysis.

Table 2 Prognostic variables with greater than three analyses reporting an association with mortality in IPAH.

Parameters	Number of supporting studies	Citation
Initial functional class (WHO or NYHA)	14	4, 14, 15, 18, 19, 21, 22, 25, 29, 33, 39, 42-44
Heart rate (sinus tachycardia)	10	14, 18, 21, 30, 36, 45-49
6 min walk test distance	8	15, 18, 19, 25, 32, 33, 35, 49
Severity of pericardial effusion	5	14, 18, 25, 47, 62
Mean pulmonary arterial pressure (mmHg)	10	4, 14, 15, 17, 25, 29, 30, 39, 47, 65
Mean right atrial pressure (mmHg)	17	14, 15, 17-19, 21, 25-27, 29, 30, 35, 36, 39, 46, 49, 56
Cardiac index (L/min/m^2)	13	4, 21, 24, 26-29, 36, 39, 42, 46, 47, 52
Stroke volume index (ml/beat/m^2)	4	19, 27, 30, 46
Pulmonary vascular resistance (dyn s cm^{-5} or wood units)	10	17, 20, 23-25, 30, 36, 42, 46, 49
Mixed venous PO_2 (mmHg) or O_2 saturation (%)	4	18, 19, 27, 56

WHO = World Health Organization; NYHA = New York Heart Association; PO_2 = partial pressure of oxygen; O_2 = oxygen.

Table 3 Significant and non-significant associations of eight parameters described to be associated with mortality in IPAH.

Prognostic factor	Number of supporting publications	Supporting citations	Number of non-supporting publications	Non-supporting citations
Mean pulmonary arterial pressure (mmHg)	10	4, 14, 15, 17, 25, 29, 30, 39, 47, 65	19	14, 15, 18-20, 22-24, 26-28, 33, 35, 36, 42, 46, 49, 52, 56
Mean right atrial pressure (mmHg)	17	14, 15, 17-19, 21, 25-27, 29, 30, 35, 36, 39, 46, 49, 56	11	17-20, 23, 24, 26, 28, 33, 47, 52
Cardiac output (L/min)	3	14, 20, 21	6	14, 21-25
Right ventricular end diastolic pressure (mmHg)	3	20, 26, 39	4	20, 26-28
Pulmonary vascular resistance [(dynes s cm^{-5} or Woods units (mmHg/L/min)]	10	17, 20, 23-25, 30, 36, 42, 46, 49	7	18, 20-22, 29, 47, 56
Functional class (WHO or NYHA)	14	4, 14, 15, 18, 19, 21, 22, 25, 29, 33, 39, 42-44	11	4, 14, 15, 18, 19, 23, 24, 28, 35, 36, 57
6 min walk test distance (m)	8	15, 18, 19, 25, 32, 33, 35, 49	4	15, 18, 23, 36
Diffusing capacity of CO (mL/min/mmHg)	1	4	2	4, 23

WHO = World Health Organization; NYHA = New York Heart Association; CO = carbon monoxide.

For mRAP, 17 studies were identified that supported this parameter as a prognostic factor for mortality in IPAH while 11 studies did not find an association (Table 5). Four studies reported an association between mRAP and mortality by some analyses but not others within the same study.[16–19] As with mPAP there was significant heterogeneity in the type of statistical analysis employed.

For cardiac output only 3 analyses were identified that supported this parameter as a prognostic factor for mortality in IPAH (Table 6).[14,20,21] Two of these studies (Nagaya et al.[14] and Wensel et al.[21]) identified an association between CO and mortality in their univariable analysis that was lost when the analysis was corrected for other factors in the multivariable analyses.[14,21] Four other studies were identified that did not find an association between CO and mortality.[22–25]

For RVEDP, only 3 studies were identified that supported this parameter as a prognostic factor for mortality in IPAH[20,26] (Ref.[15,18,38]) (Table 7). However two of these (Rozkovec et al.[20] and Kanemoto et al.[26]) also reported the absence of an association depending on the type of analysis performed or the definition of survival that was used. Two other studies did not detect any association between RVEDP and mortality.[27,28]

For PVR, 10 studies were identified that supported this parameter as a prognostic factor for mortality in IPAH while 7 studies did not find an association (Table 8). Only one study by Rozkovec and colleagues, depending on the type of analysis chosen, reported both an association and a lack of association within the same study.[20]

For functional class, 14 studies were identified that supported this parameter as a prognostic factor for mortality in IPAH while 11 studies did not find an association (Table 9). Five studies reported both association and the lack of association for functional class within the same study depending on the type of analysis used.[4,14,15,18,19] Many studies grouped functional classes together for analysis while others compared only some classes to others.

Ten studies have evaluated 6MWD for potential as a prognostic factor for mortality in IPAH. Eight studies were identified that supported this parameter as a prognostic factor for mortality in IPAH while 4 studies did not find an association (Table 10). Two of these studies reported an association by univariable analysis that was lost in the multivariable model.[15,18] There was significant variation in the unit of analysis with some studies using absolute cutoffs while others used blocks of distance such as 50 m. Many studies did not report the unit of analysis.

For DLCO, only 2 studies have evaluated and reported the prognostic power of the parameter for mortality in IPAH (Table 11).[4,23] Of those, one study found an association between this parameter and mortality by univariable analysis but the significance of the association was lost when other variables were accounted for in the multivariable analysis.[4] The only other study that evaluated DLCO did not detect an association with mortality.[23]

Discussion

Through a systematic review of the literature, we identified 107 patient related factors reported to predict mortality in IPAH. Despite this large number of studies, only 10 of these factors are supported by more than 3 studies. Sixty nine factors were described as prognostic variables for mortality in IPAH in only a single study. Mean RAP was the variable most commonly reported to be associated with mortality followed by functional class, cardiac index, heart rate, mPAP, PVR, 6MWD, pericardial effusion, mixed venous PO_2 or O_2 saturation, and stroke volume index.

Invasive hemodynamic variables were the most frequently reported group of prognostic factors in the current literature with 35 hemodynamic variables reported to have an association with mortality, 6 of which had greater than 3 supporting studies. However, mPAP, CO, and REVDP all had more analyses that did *not* find a predictive association compared to those that did. In fact, for mPAP

Table 4 Studies evaluating the relationship between survival and mean pulmonary arterial pressure in IPAH.

Study	Association	Comparison	Measured value (mean pulmonary arterial pressure)	Significance	Study Design	Number of patients
Loogen[65]	+	*t* test (independent random samples)	50.8 ± 3.4 (survivors) vs 69.0 ± 5.8 (nonsurvivors) (mean ± SE)	$P < 0.05$	RC	24
Eysmann[47]	+	Univar Cox life table analysis	53 ± 15 (survivors) vs 65 ± 15(nonsurvivors) (mean ± SD)	$P = 0.04$	CNS	26
Chapman[17]	+	Univar analysis (Wilcoxon test)	NR	$P = 0.0006$	RC	22
		Mann–Whitney *U* test and Fisher's exact test	84 (survival <12 mth) vs 61 (survival >40 mth)	$P < 0.05$		
D'alonzo[4]	+	Univar analysis (proportional hazard analysis)	OR 1.16 (1.05, 1.28)[b]	NR	PC	194
		Multivar analysis (proportional hazard analysis)	OR 1.02 (1.01, 1.03)[b]	NR		
Rajasekhar[39]	+	Student *t* test	54.9 ± 16.7 (survivors) vs 66.6 ± 17.7 (non survivors) (mean ± SD)	$P = 0.028$	RC	61
Okada[30]	+	Univar analysis (Mann–Whitney *U* test)	54.4 ± 17.0 (survivors) vs 66.5 ± 16.1 (non survivors) (mean ± SD)	$P = 0.001$	RC	223
Nagaya[14]	+	Univar analysis (Cox proportional hazard regression)	RR 1.043 (1.00, 1.088)[b]	$P = 0.0497$	PC	60
Appelbaum[29]	+	Univar analysis (proportional hazard model)	NR (reported only as affecting survival)	NR	RC	44
Sitbon[15]	+	Univar analysis (Proportional hazard model)	HR 1.72 (1.04, 2.86)[a] Cutoff <65 mmHg	$P = 0.036$	RC	178
Fijalkowska[25]	+	Univar analysis (Cox proportional hazard model)	HR 1.03 (1.0, 1.06)[b]	$P = 0.0337$	PC	36
Kanemoto[52]	–	*T* test	62.9 ± 17.8 (alive) vs 61.8 ± 16.9 (dead)	NS	CS	113
Rich[46]	–	Unpaired student *t* test	53 ± 9 (survivors) vs 74 ± 27 (nonsurvivors) (mean ± SD)	NS	PC	12
Rich[22]	–	Stepwise Cox regression analysis	NR	NS	PC	23
Rozkovec[20]	–	One tailed Fisher's exact test or Student *t* test	60.75 ± 22.43 (survival >5 yrs) vs 63.89 ± 12.31 (survival<5 yrs) (mean ± SD)	NS	RC	34
	–	Spearman's rank correlation to survival time (one tailed)	NR	NS		
Kanemoto[26]	–	Unpaired student *t* test	I 61 ± 4 (survial <3 mths)[c] vs IV 54 ± 3 (survival >24 mths)[c]	NS	CNS	87
		Unpaired student *t* test	II 58 ± 3 (survival 4–12 mths)[c] vs IV 54 ± 3 (survival >24 mths)[c]	NS		
		Unpaired student *t* test	III 58 ± 6 (survival 13–24 mths)[c] vs IV 54 ± 3 (survival >24 mths)[c] (mean ± SE)	NS		
Dolara[42]	–	Log rank test	Not correlated to survival Cutoff 50 mmHg	NR	RC	NR

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Table 4 (*continued*)

Study	Association	Comparison	Measured value (mean pulmonary arterial pressure)	Significance	Study Design	Number of patients
Sandoval[27]	–	Univar analysis (Proportional hazard model)	HR 2.08 (0.85, 5.10)[b]	$P = 0.105$	PC	61
Nagaya[14]	–	Multivar analysis (Cox regression)	NS	NS	PC	60
Chun[28]	–	Univar analysis (Cox proportional hazard model)	HR 0.98 (0.91, 1.10)[b]	$P = 0.76$	CNS	13
Paciocco[23]	–	Unpaired *t*-test	55 ± 9 (survivors) vs 59 ± 12 (non survivors) (mean ± SD)	NS	PC	34
		Multivar analysis (Cox regression)	HR 1.23 (1.03, 1.47)[b]	$P = 0.33$		
Bossone[24]	–	Univar analysis (Cox proportional hazard model)	HR 1.03 (0.98, 1.08) Per mmHg	$P = 0.25$	PC	51
Raymond[18]	–	Univar analysis (Cox proportional hazard model)	HR 1.30 (0.76, 2.24) Per 15 mmHg	$P = 0.344$	PC	81
Sitbon[15]	–	Multivar analysis (Cox proportional hazard regression)	NR	NS	RC	178
Kielstein[56]	–	2 tailed *t* test	54 ± 13 (survivors) vs 56 ± 15 (nonsurvivors) (mean ± SD)	NS	PC	57
McLaughlin[33]	–	Univar analysis (Cox proportional hazard model)	HR 1.4 (0.6, 3.6) Cutoff ≤54 mmHg	NR	PC	169
Mahapatra[36]	–	Wilcoxon rank sum test	51 ± 11 (survivors) vs 54 ± 10 (nonsurvivors)	$P = 0.3273$	PC	104
		Univar analyis (Cox proportional hazard model)	HR 1.02 (0.98, 1.05)[b]	$P = 0.2586$		
Provencher[35]	–	Univar analysis (Cox proportional hazard model)	HR 1.01 (0.96, 1.06)[b]	$P = 0.642$	RC	103
Van Wolferen[19]	–	Univar analysis (Cox proportional hazard model)	HR 1.03(0.41, 2.60)[b]	$P = 0.941$	PC	64
Henkens[49]	–	*t* test or chi-square test	53 ± 13 (survivors) vs 53 ± 16 (nonsurvivors)	$P = 0.90$	RC	140

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
All mean pulmonary arterial pressure values reported in mmHg.
Univar = univariable; Multivar = multivariable; PC = prospective cohort; RC = retrospective cohort; CS = cross sectional study; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = value not reported; OR = odds ratio; RR = relative risk; HR = hazard ratio; Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals; Mths = months; Yrs = years.

[a] inverse association (higher mortality associated with a lower mPAP).

[b] A cutoff value or number of units used for comparison was not explicitly defined.

[c] From time of right heart catheterization.

Table 5 Studies reporting evaluating the relationship between survival and mean right atrial pressure in IPAH.

Study	Association	Comparison	Measured value (mean right atrial pressure)	Significance	Study Design	Number of patients
Rich[46]	+	Unpaired student *t* test	6 ± 2 (survivors) vs 17 ± 6 (nonsurvivors) (mean ± SD)	$P < 0.01$	PC	12
Kanemoto[26]	+	Unpaired student *t* test	I 13 ± 3 (survival <3 mths)[b] vs IV 6 ± 1(survival >24 mths)[b] (mean ± SE)	$P = 0.01$	CNS	87
Chapman[17]	+	Multivar analysis (Cox proportional hazards regression)	NR	$P = 0.0307$	RC	22
Rajasekhar[39]	+	Student *t* test	6.0 ± 3.3 (survivors) vs 9.5 ± 5.6 (non survivors) (mean ± SD)	$P = 0.023$	RC	61
		Student *t* test	5.9 ± 2.2 (survival >2 years) vs 11.2 ± 5.8 (survival ≤2 years)	$P = 0.002$		
		Life table survival analysis (Lee Desu statistics)	63 mths vs 13 mths (median survival) (RAP cutoff ≤ 7 mmHg)	$P = 0.005$		
Sandoval[27]	+	Univar analysis (Proportional hazard model)	HR 3.87 (1.59, 9.44)[a]	$P = 0.004$	PC	61
		Multivar analysis (Cox Proportional hazard regression)	HR 4.30 (1.20, 15.4)[a]	$P = 0.02$		
Okada[30]	+	Univar analysis (Mann–Whitney *U* test)	5.4 ± 5.2 (survivors) vs 8.0 ± 4.9 (non survivors) (Mean ± SD)	$P = 0.001$	RC	223
Nagaya[14]	+	Univar analysis (Cox proportional hazard regression)	RR 1.153 (1.035, 1.284)[a]	$P = 0.0095$	PC	60
Appelbaum[29]	+	Univar analysis (proportional hazard model)	NR (reported only as affecting survival)	NR	RC	44
Raymond[18]	+	Univar analysis (Cox proportional hazard model)	HR 1.52 (1.13, 2.05) Per 5 mmHg	$P = 0.004$	PC	81
Sitbon[15]	+	Univar analysis (Proportional hazard model)	HR 2.74 (1.58, 4.75) Cutoff ≥12 mmHg	$P = 0.0003$	RC	178
		Multivar analysis (Cox proportional hazard regression model)	NR	NR		
Wensel[21]	+	Univar analysis (Cox proportional hazard model)	HR 1.118 (1.060, 1.179)[a]	$P = 0.0001$	PC	86
		Multivar analysis (Cox proportional hazard model)	HR 1.076 (CI NR)[a]	$P < 0.05$		
Kielstein[56]	+	2 tailed *t* test	7.5 ± 5.1 (survivors) vs 12.3 ± 7.1 (nonsurvivors) (mean ± SD)	$P < 0.05$	PC	57
Fijalkowska[25]	+	Univar analysis (Cox proportional hazard model)	HR 1.15 (1.04, 1.27)[a]	$P = 0.0045$	PC	36
		Multivar analysis (Cox proportional hazard model)	HR 15.4 (1.38, 165)[a]	$P = 0.024$		
Mahapatra[36]	+	Wilcoxon rank sum test	12 ± 6.8 (survivors) vs 16 ± 6.1 (nonsurvivors)	$P = 0.0193$	PC	104
		Univar analysis (Cox proportional hazard model)	HR 1.07 (1.01, 1.13)[a]	$P = 0.0158$		
Provencher[35]	+	Univar analysis (Cox proportional hazard model)	HR 0.90 (0.81, 0.99)[a]	$P = 0.034$	RC	103
Van Wolferen[19]	+	Univar analysis (Cox proportional hazard model)	HR 2.85 (1.15, 7.28)[a]	$P = 0.024$	PC	64
Henkens[49]	+	Independent *t* test or chi-square test	8 ± 5 (survivors) vs 11 ± 6 (nonsurvivors)	$P = 0.01$	RC	140
Kanemoto[52]	−	Student *t* test	7.2 ± 4.6 (alive) vs 9.2 ± 7.4 (dead)	NS	CS	113
Rozkovec[20]	−	One tailed Fisher's exact test or Student *t* test	8.00 ± 4.63 (survival >5 yrs) vs 7.56 ± 3.55 (survival <5 yrs) (mean ± SD)	NS	RC	34
		Spearman's rank correlation to survival time (one tailed)	NR	NS		

(*continued on next page*)

Table 5 (*continued*)

Study	Association	Comparison	Measured value (mean right atrial pressure)	Significance	Study Design	Number of patients
Kanemoto[26]	–	Unpaired student *t* test	II 6 ± 1 (survival 4–12 mths)[b] vs IV 6 ± 1 (survival >24 mths)[b]	NS	CNS	87
		Unpaired student *t* test	III 6 ± 1 (survival 13–24 mths)[b] vs IV 6 ± 1 (survival >24 mths)[b] (mean ± SE)	NS		
Eysmann[47]	–	Univar analysis (Cox life table)	9 ± 7 (survivors) vs 13 ± 7 (nonsurvivors) (mean ± SD)	$P = 0.08$	CNS	26
Chapman[17]	–	Univar analysis (Wilcoxon test)	NR	$P = 0.7560$	RC	22
		Mann–Whitney *U* test or Fisher's exact test	9 (survival <12 mth) vs 9 (survival >40 mth)	NS		
Chun[28]	–	Univar analysis (Cox proportional hazard model)	HR 1.03 (0.62, 1.17)[a]	$P = 0.89$	CNS	13
Paciocco[23]	–	Unpaired *t*-test	11 ± 6 (survivors) vs 14 ± 5 (non survivors) (mean ± SD)	NS	PC	34
		Multivar analysis (Cox regression)	HR 1.09 (0.95, 1.24)[a]	$P = 0.19$		
Bossone[24]	–	Univar analysis (Cox proportional hazard model)	RR 1.08 (1.00,1.16) Per mmHg	$P = 0.05$	PC	51
Raymond[18]	–	Multivar analysis (Cox proportional hazard model)	NR	NS	PC	81
McLaughlin[33]	–	Univar analysis (Cox proportional hazard model)	HR 1.9 (0.7, 4.8) Cutoff >8.5	NS	PC	169
Van Wolferen[19]	–	Multivar analysis (Cox proportional hazard model)	HR 1.074(CI NR)[a]	$P = 0.203$	PC	64

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
All mean right atrial pressure values reported in mmHg.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; CI = confidence interval; PC = prospective cohort; RC = retrospective cohort; CS = cross sectional study; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = value not reported; OR = odds ratio; RR = relative risk; HR = hazard ratio; Mths = months; Yrs = years.

[a] A cutoff value or number of units used for comparison was not explicitly defined.

[b] from time of right heart catheterization.

Table 6 Studies reporting evaluating the relationship between survival and cardiac output in IPAH.

Study	Association	Comparison	Measured value	Significance	Study Design	Number of patients
Rozkovec[20]	+	One tailed Fisher's exact test or Student *t* test	3.56 ± 1.14 (survival >5 yrs) vs 2.77 ± 0.44 (survival <5 yrs) (mean ± SD)	$P < 0.01$	RC	34
		Spearman's rank correlation to survival time (one tailed)	NR	$P < 0.0005$		
Nagaya[14]	+	Univar analysis (Cox proportional hazard regression)	RR 0.447 (0.226, 0.885)[a]	$P = 0.0209$	PC	60
Wensel[21]	+	Univar analysis (Cox proportional hazard model)	HR 0.684 (0.491, 0.952)[a]	$P = 0.017$	PC	86
Rich[22]	−	Stepwise Cox regression analysis	NR	NS	PC	23
Nagaya[14]	−	Multivar analysis (Cox regression model)	NR	NS	PC	60
Paciocco[23]	−	Unpaired *t*-test	4 ± 1.5 (survivors) vs 3.4 ± 1.6 (non survivors) (mean ± SD)	$P = 0.11$	PC	34
		Multivar analysis (Cox regression model)	HR 0.66 (0.38, 1.14)[a]	$P = 0.14$		
Bossone[24]	−	Univar analysis (Cox proportional hazard model)	RR 0.63 (0.39, 1.03) Per L/min	$P = 0.06$	PC	51
Wensel[21]	−	Multivar analysis (Cox proportional hazard model)	NR	NS	PC	86
Fijalkowska[25]	−	Univar analysis (Cox proportional hazard model)	HR 0.52 (0.26, 1.04)[a]	$P = 0.0661$	PC	36

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
All cardiac output values reported in L/min.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; PC = prospective cohort; RC = retrospective cohort; NS = not significant (value not provided); NR = value not reported; RR = relative risk; HR = hazard ratio; Yrs = years.
[a] A cutoff value or number of units used for comparison was not explicitly defined.

Table 7 Studies reporting the relationship between survival and right ventricular end diastolic pressure (RVEDP) in IPAH.

Study	Association	Comparison	Measured value (right ventricular end diastolic pressure)	Significance	Study Design	Number of patients
Rozkovec[20]	+	Spearman's rank correlation to survival time (one tailed)	NR	$P < 0.025$	RC	34
Kanemoto[26]	+	Unpaired student *t* test	I 13 ± 2 (survival <3 mths)[b] vs IV 8 ± 1 (survival >24 mths)[b]	$P = 0.005$	CNS	87
		Unpaired student *t* test	11 ± 1 (survival ≤2 yrs) vs 8 ± 1 (survival >2 yrs) (mean ± SE)	$P = 0.05$		
Rajasekhar[39]	+	Student *t* test	8.7 ± 4.2 (survivors) vs 13.8 ± 6.8 (nonsurvivors) (mean ± SD)	$P = 0.009$	RC	61
		Student *t* test	9.4 ± 3.2 (survival >2 yrs) vs 15.7 ± 7.1 (survival ≤2 yrs)	$P = 0.003$		
		Life table analysis (Lee Desu statistics)	63 mths vs 13 mths (median survival) (RVEDP Cutoff ≤ 10 mmHg)	$P = 0.0002$		
Rozkovec[20]	−	One tailed Fisher's exact test or Student *t* test	11.00 ± 5.91 (survival >5 yrs) vs 12.29 ± 4.38 (survival <5 yrs) (mean ± SD)	NS	RC	34
Kanemoto[26]	−	Unpaired student *t* test	II 9 ± 2 (survival 4–12 mths)[b] vs IV 8 ± 1 (survival >24 mths)[b]	NS	CNS	87
		Unpaired student *t* test	III 10 ± 1(survival 13–24 mths)[b] vs IV 8 ± 1 (survival >24 mths)[b] (mean ± SE)	NS		
Sandoval[27]	−	Univar analysis (proportional hazard model)	HR 2.34 (0.98, 5.58)[a]	$P = 0.055$	PC	61
Chun[28]	−	Univar analysis (Cox proportional hazard model)	HR 0.96 (0.79, 1.17)[a]	$P = 0.72$	CNS	13

Significance results were defined as a *p* value <0.05 and 95% confidence intervals that did not include 1.
All right ventricular end diastolic pressure values reported in mmHg.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; PC = prospective cohort; RC = retrospective cohort; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = value not reported; HR = hazard ratio; Mths = months; Yrs = years.
[a] A cutoff value or number of units used for comparison was not explicitly defined.
[b] from time of right heart catheterization.

Table 8 Studies evaluating the relationship between survival and pulmonary vascular resistance in IPAH.

Study	Association	Comparison	Measured value (pulmonary vascular resistance)	Significance	Study Design	Number of patients
Rich[46]	+	Unpaired student *t* test	20 ± 4 (survivors) vs 57 ± 31 (nonsurvivors) (mean ± SD) WU	$P < 0.01$	PT	12
Rozkovec[20]	+	Spearman's rank correlation to survival time (one tailed)	NR	$P < 0.005$	RC	34
Dolara[42]	+	Logrank test	5 year survival probability (≤15 WU vs >15 WU)	$P < 0.01$	RC	76
Chapman[17]	+	Univariate analysis (Wilcoxon test)	NR	$P = 0.001$	RC	22
		Multivar analysis (Cox proportional hazards regression)	NR	$P = 0.0017$		
		Mann–Whitney *U* test and Fisher's exact test	25 (survival <12 month) vs 13 (survival >40 month) (mean) WU	$P < 0.05$		
Okada[30]	+	Univar analysis (Mann–Whitney *U* test)	1019 ± 528 (survivors) vs 1608 ± 854 (non survivors) (mean ± SD) (dynes·sec·cm^{-5})	$P = 0.002$	RC	223
Paciocco[23]	+	Unpaired *t*-test	11.9 ± 4.7 (survivors) vs 15.5 ± 6.0 (non survivors) (mean ± SD) WU	$P = 0.04$	PC	34
		Univar analysis (Cox regression analysis)	HR 1.12 (1.01, 1.26)[b] WU	$P = 0.04$[a]		
Bossone[24]	+	Univar analysis (Cox proportional hazard model)	HR 1.11 (1.02,1.21) Per WU	$P = 0.017$	PC	51
Fijalkowska[25]	+	Univar analysis (Cox proportional hazard model)	HR 1.08 (1.0, 1.17)[b] WU	$P = 0.0321$	PC	36
Mahapatra[36]	+	Wilcoxon rank sum test	1152 ± 582 (survivors) vs 1639 ± 767 (nonsurvivors) (mean ± NR) (dynes·sec·cm^{-5})	$P = 0.0018$	PC	104
		Univar analysis (Cox proportional hazard model)	HR 1.05 (1.01,1.09)[b]	$P = 0.0038$		
Henkens[49]	+	*t* test or chi-square test	859 ± 455 (survivors) vs 1165 ± 610 (nonsurvivors) (mean ± SD) (dynes·sec·cm^{-5})	$P = 0.01$	RC	140
Rich[22]	−	Stepwise Cox regression analysis	NR WU	NS	PT	23
Rozkovec[20]	−	One tailed Fisher's exact test or Student's *t* test	16.95 ± 9.35 (survival >5 yrs) vs 20.66 ± 4.84 (survival <5 yrs) (mean ± SD) WU	NS	RC	34
Eysmann[47]	−	Univar Cox life table analysis	NR	$P = 0.08$	CNS	26
Appelbaum[29]	−	Univar analysis (Cox proportional hazard model)	Reported as lacking association (statistics not shown)	NR	RC	44
Raymond[18]	−	Univar analysis (Cox proportional hazard model)	HR 1.13 (0.82, 1.55) per 5 WU	$P = 0.458$	PC	81
Wensel[21]	−	Univar analysis (Cox proportional hazard model)	HR 1.000 (1.000, 1.001)[b]	$P = 0.006$	PC	86
Kielstein[56]	−	2 tailed *t* test	1028 ± 489 (survivors) vs 1259 ± 648(nonsurvivors) (mean ± SD) (dynes·sec·cm^{-5})	$P > 0.05$	PC	57

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
Pulmonary vascular resistance units in dyn s cm^{-5} unless otherwise stated.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; WU = woods units; PT = prospective trial; PC = prospective cohort; RC = retrospective cohort; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = value not reported; OR = odds ratio; HR = hazard ratio.

[a] not significant after adjusting for the difference between resting and trough oxygen saturation on 6 min walk test ($P = 0.06$).

[b] A cutoff value or number of units used for comparison was not explicitly defined.

Table 9 Studies evaluating the relationship between survival and functional class (New York Heart Association or World Health Organization) in IPAH.

Study	Association	Comparison	Measured value (Functional class)	Significance	Study Design	Number of patients
Rich[22]	+	Stepwise Cox regression	Regression coefficient 2.07	$P = 0.002$	PT	23
Dolara[42]	+	Log rank test	5 year survival probably 11% vs 52% Class II/III vs IV	$P < 0.001$	RC	86
D'alonzo[4]	+	Univar analysis (Cox proportional hazards model)	OR 2.38 (1.45 3.88) Class IV vs I/II/III	NR	PC	194
		Univar analysis (Cox proportional hazards model)	OR 1.93 (1.17, 3.17) Class III/IV vs I/II	NR		
Rajasekhar[39]	+	Life table survival analysis (Lee Desu statistics)	Class I 126 mths Class II 35 mths Class III 11 mths Class IV 9 mths (median survival)	$P = 0.0001$	RC	61
Nagaya[14]	+	Univar analysis (Cox regression analysis)	RR 3.922 (1.629, 9.439)[a]	$P = 0.0023$	PC	60
Appelbaum[29]	+	Univar analysis (Cox proportional hazard model)	NR Class IV vs I/II/III	$P < 0.01$	RC	44
Raymond[18]	+	Univar analysis (Cox proportional hazard model)	HR 3.25 (1.35, 7.82) Class IV vs I/II/III	$P = 0.005$	PC	81
Sitbon[15]	+	Univar analysis (Cox proportional hazard model)	HR 2.24 (1.34, 3.73) Class IV vs III	$P = 0.002$	RC	178
Wensel[21]	+	Univar analysis (Cox proportional hazard model)	NR	NR	PC	86
McLaughlin[33]	+	Univar analysis (Cox proportional hazard model)	HR 3.2 (1.1, 9.7) Class IV vs I/II/III	NR	PC	169
Barst[43]	+	Proportional hazard model	HR 5.35 (1.96, 14.56) Class IV vs III HR 8.74 (2.23, 34.21) Class IV vs II	$P = 0.001$ $P = 0.002$	PC	412
Fijalkowska[25]	+	Univar analysis (Cox proportional hazard model)	HR 5.33 (1.33, 21.4)[a]	$P = 0.0181$	PC	36
Jing[44]	+	Log rank test	Class I/II vs III/IV	$P = 0.02$	PC	72
Van Wolferen[19]	+	Univar analysis (Cox proportional hazard model)	HR 2.96 (1.34, 15.8)[a]	$P = 0.015$	PC	64
D'alonzo[4]	−	Multivar analysis (Cox proportional hazards model)	OR 1.69 (0.91, 3.13) (model 1) OR 1.67 (0.91, 3.05) (model 2) OR 1.50 (0.79, 2.83) (model 3) Class IV vs I/II/III	NS	PC	194
Nagaya[57]	−	Multivar analysis (Cox proportional hazard model)	RR 1.874 (0.853, 4.120)[a]	$P = 0.1180$	CC	90
Nagaya[14]	−	Multivar analysis (Cox regression Analysis)	RR 1.530 (CI NR)[a]	$P = 0.4761$	PC	60
Chun[28]	−	Univar analysis (Cox proportional hazard model)	HR 3.20 (0.61, 16.74) Class II/IV	$P = 0.16$	CNS	13
Paciocco[23]	−	Univar analysis (Cox regression analysis)	HR 0.60 (0.11, 3.20)[a]	$P = 0.55$	PC	34
Bossone[24]	−	Univar analysis (Cox proportional hazard model)	HR 2.04 (0.46, 8.97) Class III/IV vs II	$P = 0.347$	PC	51
Raymond[18]	−	Multivar analysis (Cox proportional hazard model)	NR	NS	PC	81
Sitbon[15]	−	Multivar analysis (Cox proportional hazard regression)	Risk ratio not reported Class IV vs III	NS	RC	178
Mahapatra[36]	−	Univar analysis (Cox proportional hazard model)	HR 0.9 (0.5, 1.6)[a]	$P = 0.6917$	PC	104
Provencher[35]	−	Univar analysis (Cox proportional hazard model)	HR 0.65 (0.14, 2,94) Class IV vs III	$P = 0.574$	RC	103
Van Wolferen[19]	−	Multivar analysis (Cox proportional hazard model)	HR 1.211 (CI NR)[a]	$P = 0.703$	PC	64

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
Class I–IV = New York Heart Association functional class or World Health Organization functional class.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; CI = confidence interval; PT = prospective trial; PC = prospective cohort; RC = retrospective cohort; CC = case control study; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = not reported; OR = odds ratio; RR = relative risk; HR = hazard ratio.
[a] A cutoff value or number of units used for comparison was not explicitly defined.

Table 10 Studies evaluating the relationship between survival and 6 min walk distance in IPAH.

Study	Association	Comparison	Measured value (6 min walk distance)	Significance	Study Design	Number of patients
Miyamoto[32]	+	Multivar analysis (Cox proportional hazard model)	HR 0.986 (0.973, 0.999) (Cutoff ≥332 m)	$P = 0.0381$	PC	43
Raymond[18]	+	Univar analysis (Cox proportional hazard model)	HR 0.36 (0.20, 0.66) (Cutoff 500 ft)	$P = 0.001$	PC	81
Sitbon[15]	+	Univar analysis (Proportional hazard model)	HR 2.20 (1.31, 3.69) (Cutoff ≤250 m)	$P = 0.003$	RC	178
McLaughlin[33]	+	Univar analysis (Cox proportional hazard model)	HR 4.0 (1.3, 12.2) (Cutoff ≤358 m)	NR	PC	169
Fijalkowska[25]	+	Univar analysis (Cox proportional hazard model)	HR 0.99 (0.98, 0.99)[a]	$P = 0.0062$	PC	36
Provencher[35]	+	Univar analysis (Cox proportional hazard model)	HR 1.42 (1.16, 1.84) (per 50 m)	$P = 0.002$	RC	103
Van Wolferen[19]	+	Univar analysis (Cox proportional hazard model)	HR 0.33 (0.15, 0.93)[a]	$P = 0.036$	PC	64
		Multivar analysis (Cox proportional hazard model)	HR 0.949 (CI NR)[a]	$P = 0.011$		
Henkens[49]	+	*t* test or chi-square test	404 ± 132 m (survivors) vs 326 ± 120 m (nonsurvivors)	$P < 0.001$	RC	140
Paciocco[23]	−	Univar analysis (Cox regression analysis)	HR 0.82 (0.63, 1.05) (per 50 m)	$P = 0.11$	PC	34
Raymond[18]	−	Multivar analysis (Cox proportional hazard model)	HR 0.56 (0.29, 1.08) (Cutoff 500 ft)	$P = 0.082$	PC	81
Sitbon[15]	−	Multivar analysis (Cox proportional hazard model)	NR (Cutoff <250 m)	NS	RC	178
Mahapatra[36]	−	Wilcoxon rank sum test	334 ± 82 m (survivors) vs 299 ± 111 m (nonsurvivors)	$P = 0.179$	PC	104
		Univar analysis (Cox proportional hazard model)	HR 0.99 (0.99, 1.00)[a]	$P = 0.1331$		

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; CI = confidence interval; PC = prospective cohort; RC = retrospective cohort; CNS = cohort type not specified or determined from the reported study; NS = not significant (value not provided); NR = not reported; OR = odds ratio; HR = hazard ratio.
[a] A cutoff value or number of units used for comparison was not explicitly defined.

Table 11 Studies evaluating the relationship between survival and diffusing capacity of carbon monoxide in IPAH.

Study	Association	Comparison	Measured value (diffusing capacity)	Significance	Study Design	Number of patients
D'alonzo[4]	+	Univar analysis (Cox proportional hazard model)	OR 0.97 (0.94, 0.99) Per unit of measurement (units not defined)	NR	PC	194
D'alonzo[4]	−	Multivar analysis (Cox proportional hazard model)	OR 0.99 (0.96, 1.02) (model 1) OR 0.96 (0.93, 1.00) (model 2) OR 0.97 (0.94, 1.00) (model 3) All per unit of measurement (units not defined)	NR	PC	194
Paciocco[23]	−	Univar analysis (Cox regression analysis)	HR 0.99 (0.93, 1.05)[a]	$P = 0.74$	PC	34

Significance results were defined as a p value <0.05 and 95% confidence intervals that did not include 1.
Diffusing capacity of carbon monoxide in reported mL min^{-1} $mmHg^{-1}$
Bracketed numbers following odds ratios or hazard ratios indicate 95% confidence intervals.
Univar = univariable; Multivar = multivariable; PC = prospective cohort; NR = not reported; OR = odds ratio; HR = hazard ratio.
[a] A cutoff value or number of units used for comparison was not explicitly defined.

there were almost twice as many analyses that evaluated this variable and did *not* find a significant association with mortality compared to those that did find an association with mortality. Mean RAP and PVR were the only hemodynamic variables that had more supporting than non-supporting analyses.

In 1980 the National Institutes of Health (NIH) established a registry for primary pulmonary hypertension and prospectively followed the natural history of this disease over a 5 year period in 194 patients.[4] In an attempt to develop a clinically useful means of prognosticating mortality in IPAH the NIH registry cohort was retrospectively analyzed in 1991 at which time a number of variables associated with poor survival were identified including higher New York Heart Association functional class, the presence of Raynaud phenomenon, elevated mRAP, elevate mPAP, decreased cardiac index (CI), and a reduced DLCO.[4] From this analysis an equation was developed to predict survival base solely on hemodynamic parameters (mRAP, mPAP pressure, and CI).

While the NIH equation is attractive in its simplicity, validity represents a major concern with the use of this tool to prognosticate mortality in IPAH. In 1994 Sandoval and colleagues attempted to prospectively validate the NIH formula in a cohort of 60 patients with primary pulmonary hypertension (PPH)[27] and found that while it was highly sensitive at predicting survival in PPH, it lacked specificity. Similarly, Appelbaum et al. compared the NIH projected and actual survival times of 44 patients with PPH in Israel and found a poor correlation between real and projected survival times.[29] In 1999 Okada et al. developed an alternate survival equation based on retrospective survey of 223 PPH patients in Japan.[30] Unfortunately the Japanese equation has not been prospectively validated and was not compared to the NIH equation. More recently Thenappan et al. analyzed 282 patients with idiopathic, familial and anorexigen-associated PAH in the Pulmonary Hypertension Connection registry and found that survival in the current era is significantly better than that predicted by the NIH equation.[31] These authors also used their database to generate a new survival equation (using the same parameter of mPAP, mRAP, and CI). However, this new equation is yet to be prospectively validated. More recently the REVEAL Registry (Registry to Evaluate Early And Long-term pulmonary arterial hypertension disease management) has been established to provide epidemiologic data on the diagnosis, treatment, and management of PAH. However, at the current time only baseline data has been published and no mortality analysis has been reported in the peer reviewed literature (Chest prepublished online 16 Oct 2009 doi:10.1378/chest.09-1140).

Both the NIH and the Japanese survival equations are based primarily on hemodynamic parameters obtained on right heart catheterization. The reliance on cardiac catheterization data to prognosticate disease severity and mortality is not optimal as this invasive procedure is not without associated morbidity. Furthermore this procedure is a costly and a limited resource in many health care systems. Given these limitations, not only is initial assessment more difficult but follow-up evaluations cannot routinely include obtaining this hemodynamic data as frequent re-catheterization is not feasible.

One of the greatest difficulties in comparing any given prognostic factor across studies is the variability in the analysis used. The most commonly employed method of statistical analysis in the reviewed publications was the Cox proportional hazard model. However, even within this method there was significant variation in the techniques and definitions employed. An example of this can be seen in the evaluation of the 6MWD. Of the 10 studies identified that evaluated this factor, 8 used the Cox proportional hazard model. However, even within this method, one study used a cutoff value of 332 m,[32] one used 500 ft,[18] one used 250 m,[15] one 358 m,[33] two used 50 m increments,[34,35] and three did not define the unit of analysis.[19,25,36] Furthermore, some investigators,[33,23,36,35] used a univariable analysis, while other investigators[32] reported the results of their multivariable analysis only. Van Wolferen et al.[19] found an association in both the univariable and multivariable analysis, but both Raymond et al.[18] and Sitbon et al.[15] found that this variable was significant in their univariable analysis but the not the multivariable analysis. These variations in analytical methods and attendant findings make qualitative comparisons difficult and quantitative ones impossible.

It is important to emphasize that studies that fail to show a significant association do not necessarily provide evidence for non-association on an individual basis. In particular very few of these studies were specifically designed or sufficiently powered to test a particular association. On the other hand, the identification of a significant associated frequently occurred within the context of studies that evaluated multiple factors simultaneously without an *a priori* hypothesis stating the primary variable of interest and without correcting for multiple comparisons. This places the studies at risk for a spurious correlation.

Many studies evaluated in this review were excluded because variables were explored in mixed populations of PAH. Studies often include multiple subgroups of PAH (category 1 of the Venice or Dana Point classification) in their cohorts and subsequent analyses. Although this approach may be appropriate in some therapeutic studies, the validity of this practice when evaluating prognostic factors is questionable. It is well known that survival curves are not equivalent across all subgroups of category 1 PAH[37] and therefore it should not be assumed that prognostic variables will perform the same for these different populations.

We did not perform a formal meta-analysis of the data. There was significant heterogeneity across the studies with regards to study populations, study design, analytical techniques, and reporting of methods. It would be inappropriate to meta-analyze the data in the face of this degree of heterogeneity.

We did not include surrogate markers of prognostic variable in the synthesis of this review. For example a study by Raeside et al.[38] described a correlation between cardiopulmonary exercise (CPET) parameters and mPAP but was not included. If mPAP was conclusively shown to be a predictor of early mortality, and CPET variables were correlated with mPAP, than exercise testing may be a useful tool for evaluation as it is a less invasive approach compared to cardiac catheterization. However, as shown in this review, the utility of mPAP is controversial and therefore it is premature to infer the value of CPET parameters in predicting early mortality based on correlations with mPAP rather than evaluating the predictive power of these variables on mortality directly as was done by Wensel and colleagues.[21]

Conclusion

IPAH is a severe and life limiting disease. The last two decades have seen growing awareness of this condition, improved understanding of IPAH pathophysiology, and the development of multiple treatment options. Despite these advances it remains difficult to accurately predict the clinical course of IPAH patients and thus determine the most appropriate strategy for monitoring, intervention, and timely referral for lung transplantation. With the advent of numerous potentially beneficial intervention strategies, the need to identify those at greatest risk for adverse outcomes has become increasingly important. There is a large body of literature describing numerous factors that predict early mortality in IPAH however consensus on the most valuable factors has been hampered by disparate studies with small sample sizes, mixed populations, the use of composite endpoints, and variable study designs and analytical methods. These discrepancies highlight the need to evaluate the literature in total when considering the utility of variables as prognostic factors in IPAH.

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Conflict of interest statement

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